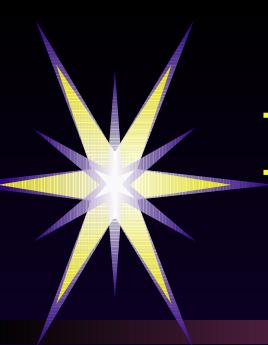


CHRONIC COMPLICATIONS IN DIABETES MELLITUS

CPT Thomas Oliver, M.D.
Endocrinology, Diabetes and
Metabolism Service
Walter Reed Army Medical
Center



DM COMPLICATIONS



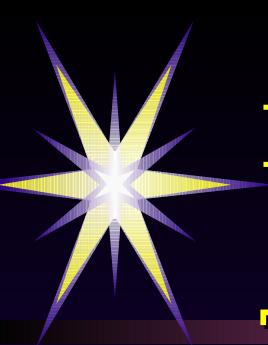
DM COMPLICATIONS

- EPIDEMIOLOGY

- ◆ MAJOR DETERMINING

FACTORS

- ❖ Duration
- ❖ Glycemic Control
- ❖ Type 1 vs. Type 2

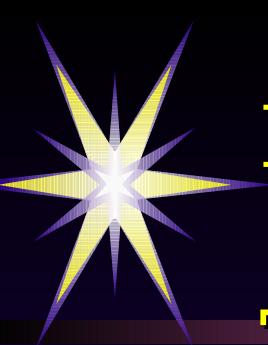


DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 1

- ◆ **DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)**
 - ❖ 1441 pts. with type 1 DM
 - ❖ 726 within 5 years of onset = 0 comp's
 - ❖ Comparison of intensive therapy vs.... conventional therapy
 - ❖ Mean follow-up 6.5 years (4-9) with 98% data collection

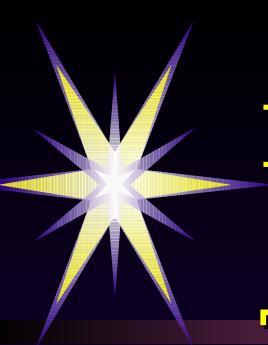


DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 1

- ◆ **DIABETES CONTROL AND
COMPLICATIONS TRIAL (DCCT)**
- ◆ **INTENSIVE THERAPY MEANS**
 - ❖ **Subcutaneous Continuous Insulin
Injection (pump) OR**
 - ❖ **Multiple daily injections AND**
 - ❖ **Monthly clinic visits**

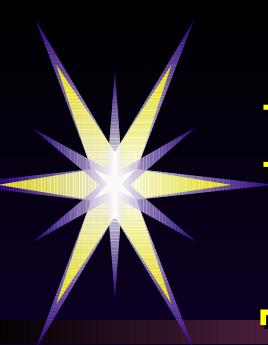


DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 1

- ◆ **DCCT RESULTS:**
- ◆ **INTENSIVE GROUP:**
 - ❖ HgA1c avg..... 7.2%
 - ❖ FS avg..... 155 mg/dl
- ◆ **CONVENTIONAL GROUP:**
 - ❖ HgA1c avg..... 9.1%
 - ❖ FS avg..... 231 mg/dl

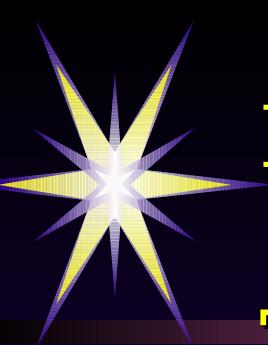


DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 1

- ◆ DCCT RESULTS:
- ❖ In Intensive Group:
- ❖ Retinopathy progressed by 3 steps in 70.3% fewer patients.
- ❖ Initial appearance of retinopathy was reduced by 27%.
- ❖ Need for laser photocoagulation reduced by 56%.

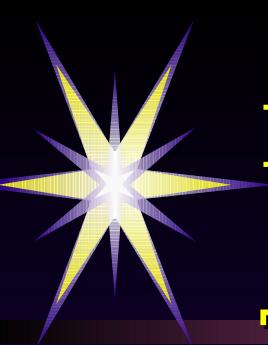


DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 1

- ◆ **DCCT RESULTS:**
- ❖ In Intensive Group:
- ❖ **Nephropathy (albuminuria > 300 mg/d) reduced by 54%.**
- ❖ **Neuropathy (Nerve conduction abnormalities + clinical sx.) reduced by 64%.**

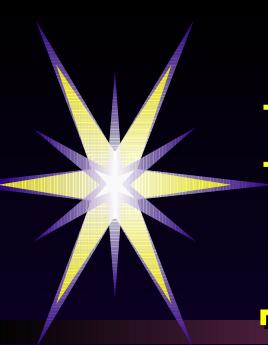


DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 1

- ◆ DCCT RESULTS:
 - ❖ In Intensive Group:
 - ❖ Macrovascular events (cardiac & peripheral) reduced; though not to statistically significant level.
 - ❖ Significant LDL elevation (>160 mg/dl) reduced by 35%.



DM COMPLICATIONS

- GLYCEMIC CONTROL IN

TYPE 2

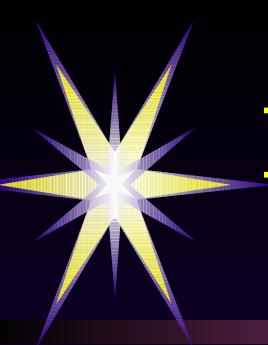
- ◆ DCCT looked at Type 1 only!
- ◆ Can we apply findings to type 2?
- ◆ Studies:
 - ❖ Small Japanese study with 110 patients shows results similar to DCCT.
 - ❖ UKPDS



- Microvascular Disease
 - Delayed retinopathy
 - Delayed nephropathy
- Macrovascular Disease
 - No effect on:
 - Cardiovascular disease
 - Diabetes-related deaths
 - All-cause mortality
 - Difference in HGB-A1C(0.9%)



- Macrovascular Disease
 - Metformin + Sulfonylurea detrimental
- Metformin monotherapy showed significant benefit on:
 - Cardiovascular disease
 - Diabetes-related death
 - All cause mortality



DM COMPLICATIONS

- MECHANISMS

- ◆ Many different tissues involved - nerves, skin, retina, kidney, heart, brain.
- ◆ Common to all of these are:

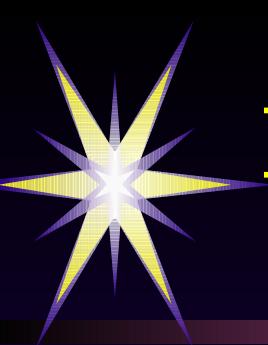
BLOOD VESSELS



DM COMPLICATIONS

- MECHANISMS

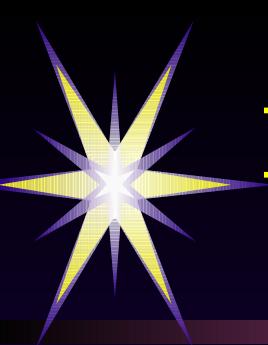
- ◆ **Microvascular Damage Affects:**
 - ❖ **Retinas**
 - ❖ **Glomeruli**
 - ❖ **Nerves**



DM COMPLICATIONS

- MECHANISMS

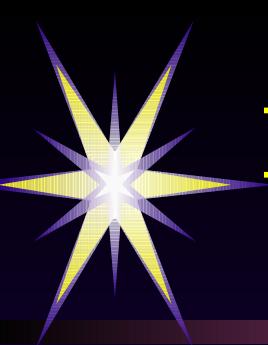
- ◆ **Microvascular Damage Causes:**
 - ❖ **Blindness**
 - ❖ **End-Stage Renal Disease**
 - ❖ **Neuropathy >>> Amputations**



DM COMPLICATIONS

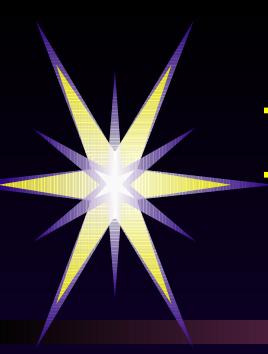
- MECHANISMS

- ◆ **Macrovascular Damage Affects Large (Named) Arteries:**
 - ❖ **Coronary Arteries**
 - ❖ **Carotid/Cerebral Arteries**
 - ❖ **Lower Extremity Arteries**



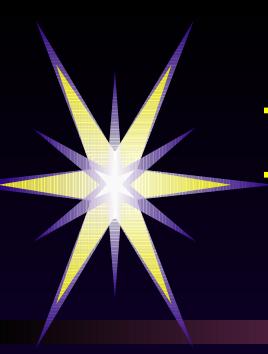
DM COMPLICATIONS - MECHANISMS

- ◆ **Macrovascular Damage Causes:**
 - ❖ **Angina, Myocardial Infarction,
Sudden Death**
 - ❖ **Strokes**
 - ❖ **Poor Healing from Wounds or
Infections >>> Amputations**



DM COMPLICATIONS - MECHANISMS

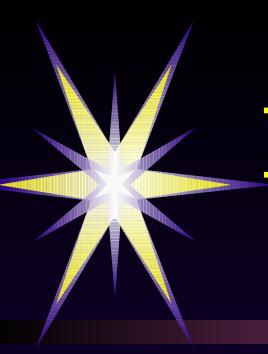
- ♦ So HOW does diabetes damage blood vessels?
- ♦ Best understood mechanism is by non-enzymatic glucosylation (glycation) of proteins and other macromolecules.
- ♦ Other mechanisms postulated include changes in NADP+ and NADH levels associated with alternative glucose metabolic fates when usual pathways are saturated.



DM COMPLICATIONS

- MECHANISMS

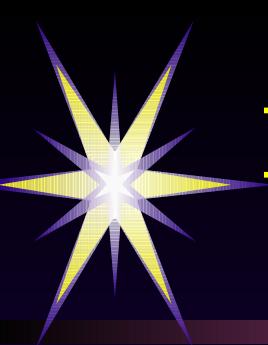
- ◆ Chronic hyperglycemia causes increased glycation of proteins, resulting in Advanced Glycation Endproducts (AGEs)
- ◆ These can cause damage through loss of function, turning on/off signal pathways within cells, or alteration in gene expression.



DM COMPLICATIONS

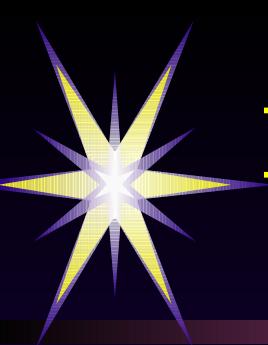
- MECHANISMS

- ◆ One of the proteins which is glycated is Hemoglobin. Because it is found in the blood, it is convenient to measure as HgA1c.
- ◆ Because RBCs (and thus Hg) survive in the blood for 90-120 days, the HgA1c provides a means to assess glycemic control over this period.



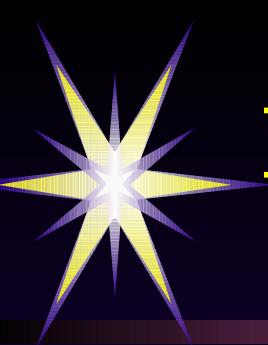
DM COMPLICATIONS - MECHANISMS

- ♦ The Role of Insulin
 - ❖ High insulin levels as seen in insulin resistance MAY be contributory to the development of:
 - ♦ Hypertension
 - ♦ Atherosclerosis



DM COMPLICATIONS - MECHANISMS

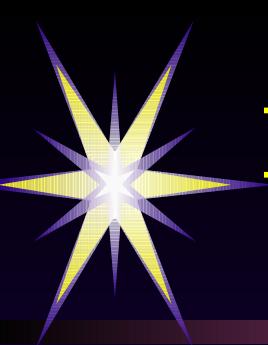
- ♦ The Role of Insulin
 - ❖ Hyperglycemia causes complications
 - ❖ Insulin causes complications
- ♦ Type 1
 - ❖ Usually not hyperinsulinemic; therefore concentrate on controlling hyperglycemia.
- ♦ Type 2 (Actively under investigation)
 - ❖ Unclear whether increasing insulin to achieve normal sugars overall benefit!!!



DM COMPLICATIONS

- EYE DISEASE

- ◆ **8,000 new cases of blindness due to DM per year in the US.**
- ◆ **12% Cases of new blindness due to DM.**
- ◆ **Leading Cause of new Blindness in working-aged Americans.**



DM COMPLICATIONS

- EYE DISEASE

- ◆ Early Changes (normal exam)
 - ❖ Loss of Autoregulation of blood flow.
 - ❖ Decreased blood flow.
 - ❖ Loss of pericytes (supporting cells).



DM COMPLICATIONS

- EYE DISEASE

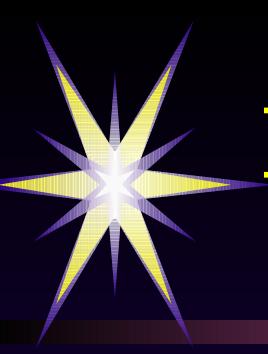
- ◆ **Nonproliferative Changes:**
 - ❖ Dot & blot hemorrhages
 - ❖ Cotton-wool spots
 - ❖ Venous Loops
 - ❖ Venous Tortuosity
- ◆ **100% incidence at 15 years**
 - ❖ Increased retinal blood flow.
 - ❖ Capillary Dropout



DM COMPLICATIONS

- EYE DISEASE

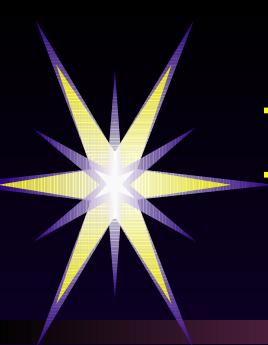
- ◆ **Proliferative Changes**
 - ❖ **Neovascularization** - most prominent at border between perfused and nonperfused retina.
 - ❖ **Vitreous hemorrhage** due to fragility of new vessels.
 - ❖ **Contraction** of co-existing glial tissue may lead to retinal detachment.



DM COMPLICATIONS

- EYE DISEASE

- ♦ **Quiescent Stage**
 - ❖ End of Proliferative changes; vision usually stable at whatever level of loss was sustained during proliferative phase.
 - ❖ Laser photocoagulation seems to accelerate transition from proliferative phase to quiescent phase. Intent is to arrive at quiescent phase with minimal loss of vision.



DM COMPLICATIONS

- EYE DISEASE

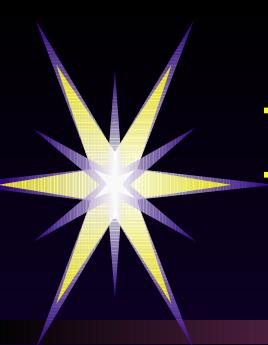
- ◆ **Macular Edema**
 - ❖ In DM, retinal vessels are more permeable.
 - ❖ Fluid leakage from vessels to retina can cause localized edema.
 - ❖ If present in the macula, can cause reduction in VA ($20/20 > 20/50$).
 - ❖ Affects 300,000 pts/year.
 - ❖ Risk can be decreased with laser rx.



DM COMPLICATIONS

- EYE DISEASE

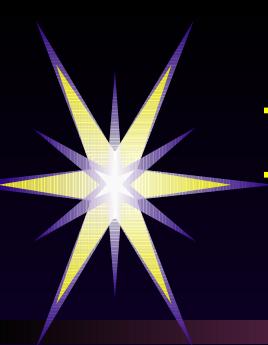
- ◆ **PREVENTION STRATEGIES:**
 - ❖ Glycemic Control
 - ❖ Regular Eye Exams
 - ❖ Photocoagulation for Macular Edema or Neovascularization



DM COMPLICATIONS

- KIDNEY DISEASE

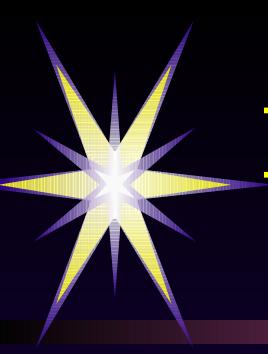
- ◆ **Leading Cause of End Stage Renal Disease (ESRD) in developed nations.**
- ◆ **27.2% Dialysis Patients have DM.**
- ◆ **36.4% NEW ESRD cases are related to DM.**
- ◆ **Familial clustering occurs.**



DM COMPLICATIONS

- KIDNEY DISEASE

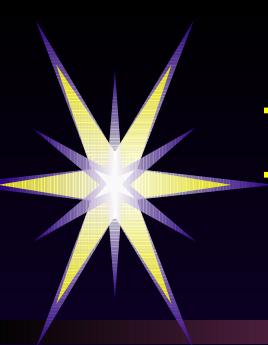
- ◆ Type 1 vs. Type 2
 - ❖ Previous studies suggested higher rate of ESRD in Type 1 pts.
 - ❖ More recent studies suggest ESRD rate in Type 2 pts. approaching that in Type 1 pts.



DM COMPLICATIONS

- KIDNEY DISEASE

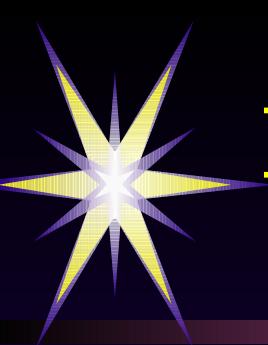
- ◆ To B (for biopsy) or not to B
- ◆ Not needed in typical cases (~ 80%)
 - ❖ DM > 10 years
 - ❖ Other “opathies” present
 - ❖ Gradual progression
- ◆ Helpful in atypical cases
 - ❖ Within 10 yrs. onset of DM
 - ❖ Other indicators of inflammatory process
 - ❖ Rapid Progression



DM COMPLICATIONS

- KIDNEY DISEASE

- ◆ **Progression in Type 1 DM**
- ◆ **Glomerular Hyperfiltration**
 - ❖ **Renomegaly**
 - ❖ **GFR up to 140% of normal**
 - ❖ **Intermittent microalbuminuria
(with hyperglycemia)**



DM COMPLICATIONS

- KIDNEY DISEASE

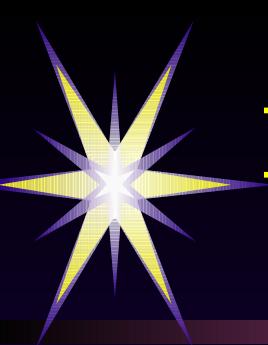
- ◆ **Progression in Type 1 DM**
- ◆ **Early Glomerular Lesions**
 - ❖ **Basement Membrane Thickening**
 - ❖ **Exercise-Induced Microalbuminuria**
 - ❖ **Begins ~ 18-24 months after onset DM**
 - ❖ **Lasts 4-15 years**



DM COMPLICATIONS

- KIDNEY DISEASE

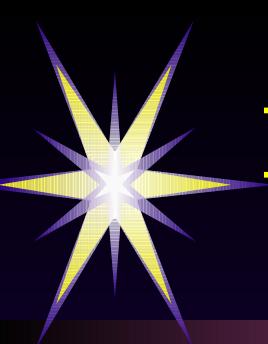
- ◆ Progression in Type 1 DM
- ◆ Microalbuminuric Stage
 - ❖ 30 - 300 mg Albumin/Day
 - ❖ GFR usually maintained
 - ❖ Associated with other organ damage



DM COMPLICATIONS

- KIDNEY DISEASE

- ◆ Progression in Type 1 DM
- ◆ Clinical nephropathy
 - ❖ > 300-500 mg/day
 - ❖ Falling GFR (~1 ml/min/month)
 - ❖ Nephrotic Syndrome may occur
 - * >3500 mg/day * Hypoalbuminemia
 - * Edema * Hyperlipidemia



DM COMPLICATIONS

- KIDNEY DISEASE

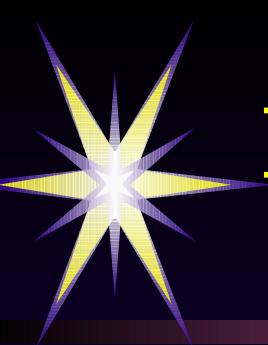
- ◆ **Progression in Type 1 DM**
- ◆ **E nd S tage R enal D isease**
 - ❖ Type 1 - 30-40% pts. after 20-30 years.
 - ❖ **Onset within 2-3 years after nephrotic syndrome.**



DM COMPLICATIONS

- KIDNEY DISEASE

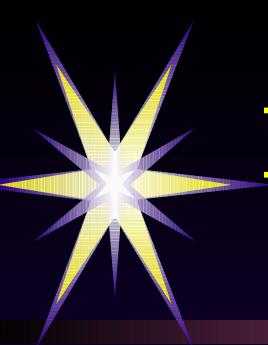
- ◆ **Progression in Type 2 DM**
- ◆ **Not as well-defined as for Type 1 due to unknown onset in many individuals.**
- ◆ **20-37% have microalbuminuria AT TIME OF DIAGNOSIS.**
- ◆ **Subgroups at higher risk include African-Americans, Hispanics, and Pima Indians.**



DM COMPLICATIONS

- KIDNEY DISEASE

- ◆ **Prevention Strategies:**
 - ❖ **Normalize Blood Pressure**
 - ❖ **Goal 120-130/80-85**
 - ❖ **ACE inhibitors particularly beneficial**
 - ❖ **Dietary Protein Restriction**
 - ❖ **0.6-0.8 gm/kg/day in established macroalbuminuria or falling GFR**
 - ❖ **Glycemic Control**
 - ❖ **Regular Monitoring for Nephropathy**
 - ❖ **Avoid Nephrotoxins (NSAIDs, some abx)**



DM COMPLICATIONS

- NEUROPATHIES

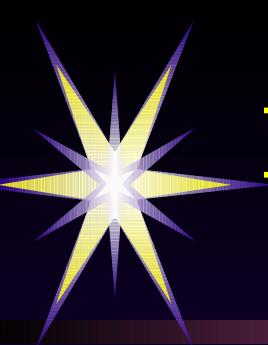
- ◆ **CNS Complications:**
- ◆ **Stroke**
 - ❖ **Increased Risk (independent of HTN, etc.)**
 - ❖ **Worsened neurologic injuries/deficits**
- ◆ **Diabetic Encephalopathy**
 - ❖ **Subtle cognitive defects**
 - ❖ **Possible increased risk from repeated episodes of severe hypoglycemia**
- ◆ **CNS infections - Mucormycosis**



DM COMPLICATIONS

- NEUROPATHIES

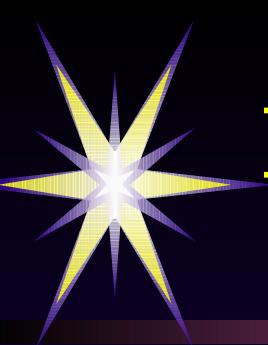
- ◆ Peripheral Neuropathies:
 - ❖ Sensory Loss
 - ◆ Pain Reception
 - ❖ Pain, Paresthesias
 - ❖ Loss of Sensation, Occult Injuries/Ulcers
 - ❖ Position/Vibratory Sense
 - ❖ Ataxia
 - ❖ Increased Falls Risk



DM COMPLICATIONS

- NEUROPATHIES

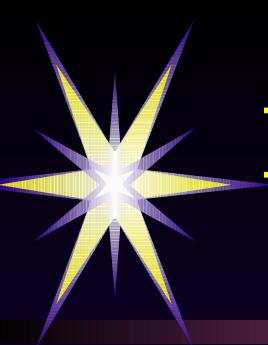
- ◆ **Peripheral Neuropathies:**
 - ❖ **Motor Neurons**
 - ◆ **Proximal Motor Neuropathy**
 - ❖ **Pain/Anesthesia anterior thigh**
 - ❖ **Difficulty rising from squat/ climbing stairs**
 - ❖ **Knee Buckling**



DM COMPLICATIONS

- NEUROPATHIES

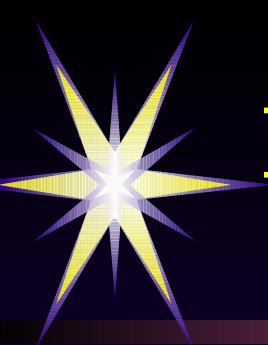
- ◆ **Autonomic Neuropathies:**
 - ❖ **Cardiovascular**
 - ◆ **Postural Hypotension**
 - ◆ **Resting Tachycardia**
 - ◆ **Painless MI**
 - ❖ **Respiratory**
 - ◆ **Sleep Apnea**



DM COMPLICATIONS

- NEUROPATHIES

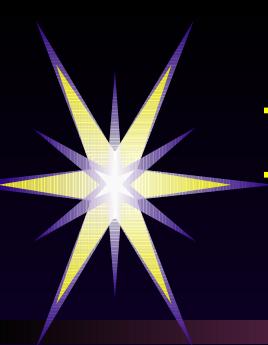
- ◆ **Autonomic Neuropathies:**
 - ❖ **GastroIntestinal**
 - ◆ **Esophageal Dysmotility**
 - ◆ **Gastroparesis**
 - ◆ **Pylorospasm**
 - ◆ **Intestinal - Diarrhea, Spasm**
 - ◆ **Gall Bladder Contractility**
 - ◆ **Anorectal Dysfunction - Incontinence**



DM COMPLICATIONS

- NEUROPATHIES

- ◆ **Autonomic Neuropathies:**
 - ❖ **GenitoUrinary**
 - ◆ **Bladder Dysfunction**
 - ◆ **Male Impotence**
 - ◆ **Ejaculatory Disorders**
 - ◆ **Reduced Vaginal Lubrication,
Dyspareunia**



DM COMPLICATIONS - NEUROPATHIES

- ◆ Prevention Strategies
 - ❖ Glycemic Control
 - ❖ Smoking Cessation
 - ❖ Regular Sensory Exams
 - ❖ Personal Protection
 - ❖ Consider Revascularization
 - ❖ Aggressive Treatment and Follow-Up of any Ulcers



DM COMPLICATIONS

- SUMMARY

**Diabetes is a leading cause
of blindness, kidney failure,
amputation, heart attack,
stroke, and premature death.**



DM COMPLICATIONS - SUMMARY

These complications can be minimized!

- ▷ Glycemic Control Matters
- ❖ Early Diagnosis of DM
 - ◊ Glycemic Control Matters
- ❖ Monitoring for complications
 - ◊ Glycemic Control Matters
- ❖ Aggressive treatment of co-risk factors
 - ◊ Glycemic Control Matters
- ❖ Team approach - access to multiple specialists



DM COMPLICATIONS - SUMMARY

Glycemic Control Matters*

Thoughtfully applied in Type 2



DM COMPLICATIONS - SUMMARY

**Prevention
is more rewarding
than
Management
of Complications**